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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
SHEINBERG, MONIKA B

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 01/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/806,325	SYKES ET AL.	
	Examiner	Art Unit	
	Monika B Sheinberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *4-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-18* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Detailed Action*.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I (claims 1-3) in the response filed September 26, 2003 is acknowledged. The traversal is on the ground(s) that a search of all the claimed subject matter would not be an undue search burden upon the examiner. This is not found persuasive because applicant did not a substantial argument distinctly and specifically point out the supposed errors in the restriction requirement. The requirement is still deemed proper and is therefore made FINAL.

Claims 4-18 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

- Claims 1-3 are hereby examined.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

- Claims 1-3 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Ex parte Forman, 230 USPQ 546 (BPA 1986) and reiterated by the Court of Appeals in In re Wands, 8 USPQ2d 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include:

Breadth of the claims,
Nature of the invention,
Amount of direction or guidance present,
Presence or absence of working examples,
State of the prior art, Predictability or lack thereof in the art,

Quantity of experimentation needed, and

The Board also stated that although the level of skill in molecular biology is high, the results of experiments in genetic engineering are unpredictable. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

The Breadth of the Claims

In the instant case, the breadth of the claims is very broad encompassing a method for the identification of any individual with any varying level of susceptibility to osteoarthritis (OA) by the loci D11S937 on chromosome 11 that is not the loci for susceptibility to OA.

The Nature of the Invention

The nature of the invention is a method for the validation of loci D11S937 as a determinative loci close enough to the susceptibility loci of OA on chromosome 11 to identify an individual predisposed to OA, specifically a female with OA of the hip.

The Amount of Direction or Guidance Present

The direction required in the instant specification is that the method claimed can predictably or at least with reasonable amount of success perform the diagnosis of an individual with the predisposition to the complex disease OA based upon a 'close' enough loci to determine susceptibility to OA. However, the specification presents uncertainty as to whether it could predictably decide the susceptibility of an individual to develop OA as seen within the specification that the allele of interest is not even *the* susceptibility locus, it is merely 'nereby' but not just there:

> This data indicates that the OA susceptibility locus on llq is **located close to** D11S937 and that the 258bp allele of D11S937 **may be present** on a predisposing ancestral chromosome. (p. 4, lines 17-20)
>
> Our linkage and association results therefore indicate that the OA susceptibility locus on llq is **located close to** D115937 and that the 258bp allele of D115937 **may be present** on an ancestral chromosome that harbours a casual DNA variant. (p. 15, lines 12-16)

With indefinite language such as "close to" and "may be present", the specification fails to identify specifically the susceptibility of OA, let alone a female with specifically OA of the hip.

As such the specification has failed to specifically allocate a diagnostic region that when used within a basic method of detection does not provide a predictable or reliable result. For example, if the locus that is actually responsible for determining susceptibility is absent yet the D11S937 is present, false results and analysis would be provided not only to those performing the analysis but also the individual patient in question. That which the Applicant claims to determine susceptibility on the chromosome is not enabled for performing the task. The specification states that as a complex disease many factors are encompassed within the development OA, therefore the mere detection of an allele 'close to' a potential locus of susceptibility that can only 'may be' indicate that there's a chance of developing OA does not qualify as a determinative, predictable and clear guidance to the determination of an individual's susceptibility to OA.

In addition, the specification fails to define any level of susceptibility thus the method is incomplete due to the failure to define the level/degree of susceptibility assessment. Nowhere in the claim is the there an assessment step that correlates the presence or absence with having the potential or susceptibility of OA. In determining whether a person is susceptible is pendant upon the presence or absence of the specified allele, the specification fails to teach or suggest what the results are determinative of: does the presence or absence determine the individual will not have any chance of developing OA or a simply a much lower chance (i.e. 2%) than typical; or in the reverse, the determinative of being 100% chance of developing OA or simply 75% greater chance than others; etc. The specification must provide adequate guidance such that one of skill in the art could practice the invention without undue experimentation. As the specification and claims are written, the instant application is an invitation to further investigate the probability of correlating OA susceptibility with that of the presence of the specified locus of D11S937 of chromosome 11 and to determine what degree of susceptibility is predictable.

The Presence or Absence of Working Examples

While working examples are not, per se, required, the specification must provide adequate guidance such that one of skill in the art could practice the invention without undue experimentation. The specification is conflicting as to whether a clear statistically significant correlation exists between the indicated locus and its association to OA (see table 3 versus page 14 line 30). Given the lack of descriptive working examples in the specification, and the

unpredictability of mapping determinative loci of disease predisposition, the specification, as filed is not enabling for the method of identifying an individual susceptible to OA based upon the D11S937 loci of chromosome 11 as claimed.

The State of the Prior Art

The state of the prior art with respect to using D11S937 as a determinative marker of identifying an individual susceptible to OA at the time of filing and afterwards points to contradicting and weakening information supporting the unpredictability of the method claimed.

For example, Chapman et al (*Am. J. Hum. Gen.*, 1999) clearly states an uncertainty of the reliability in selecting various loci (D11S937 included) on chromosome 11 for determining susceptibility of osteoarthritis (OA), however that they may be likely to be the determinative loci:

> "we have identified on chromosome 11q a region that is likely to contain a osteoarthritis-susceptibility locus" (p. 171, 2nd column, last paragraph).

However, later in the same paragraph (continued on to p. 172) chromosome 2 had been demonstrating similar results:

> "This phenomenon was also observed for one other genome marker, D2S202. Interestingly, the chromosome 2 region to which this marker maps (2q31-q32.1) has previously been identified as a region that may harbor an osteoarthristis-susceptibility locus".

A later reference including the inventors themselves, continues the uncertainty in relying upon the statement that the specified region of chromosome 11 is determinative of osteoarthritis susceptibility, in that chromosome 6 is under investigation instead:

> "COL9A1 [6q12-q13] may therefore be a susceptibility locus for female hip OA" (abstract; Mustafa et al 2000).

More recently, the inventors published a more detailed analysis of chromosome 11 (Chapman et al., *Arthritis Rheum* 2002), failing to support the instant applications claim to D11S937's determinative ability of a single locus capable of OA susceptibility (let alone specific to the hip) in addition to stating the state of the art's continued unpredictability:

> "Choosing OA candidate genes is not straightforward; the susceptibility could reside in any number of genes [...] furthermore, there is uncertainty over which joint tissue (s) is initially involved in the disease

> process[…] Clearly, for a complex diseases like OA, more than one joint tissue type may play a role, and more than one physiologic or metabolic pathway could be involved" (p. 1783, column bridging paragraph).

In addition, the above reference demonstrates that from the time of filing the instant application, further experimentation has been required and is still in progress.

The Predictability or Lack Thereof in the Art

The instant claimed invention is highly unpredictable as demonstrated above in the discussion of the state of the art. Hence, in the absence of a teaching the levels of susceptibility of the potentially determinative loci D11S937; and in the absence of the actual susceptibility locus, one of skill in the art is unable to fully determine an individual's susceptibility to OA. There is no predictability even in view of the high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of skill in the art from practicing the invention without undue experimentation.

Quantity or Experimentation needed

The quantity of experimentation needed is undue experimentation. One of skill in the art would need to perform an exhaustive search and a large amount of experimentation to determine which a more fine tuned map of the susceptibility locus/loci that render one skilled in the art capable of identifying an individual as instantly claimed in order to practice the claimed invention. In addition, more experimentation would be necessary with respects to those loci that tissue specific as required by claim 2, and/or sex specific as seen in claim 3. One of skill in the art would then have to perform undue experimentation to determine whether the resulting genetic analysis would directly lead to a predictable phenotypic analysis (OA susceptibility). As an unpredictable art, such experimentation require a high quantity of experimentation through trial and error as further demonstrated by Chapman et al. (1999; inventors). The instant application is utilizing D11S937 as merely an investigative tool as clearly stated in reference as directed to the loci selected for potentially determining the susceptibility to OA (including D11S937):

> These are a starting point for the identification of single-nucleotide polymorphisms, which can be used to narrow the interval and to define the osteoarthristis locus more precisely. (1st column, 1st paragraph).

The instant claims are an invitation to experiment as to which loci within the genome actually are determinative of OA susceptibility. Without evidence as to the correlation between specific loci and the predisposition to the disease OA, the skilled artisan would be required to practice undo experimentation to determine the specific locus/loci predictably responsible for the varying degrees of the potential occurrence of OA and which tissues would be involved.

The level of the Skill in the Art

The level of skill in the art is high. However, due to the unpredictability in directed predicting disease predisposition of a complex disease such as OA, it is noted that each embodiment of the invention is required to be individually assessed for specific locus or loci combinations that result in a predictable prognosis of OA susceptibility of any individual let alone, of females specifically at the hip. Thus it is unpredictable in view of the high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of skill in the art from practicing the invention without undue experimentation.

Thus, the specification fails to provide sufficient support of the broad method of the diagnosis disease predisposition based upon determinative loci. As a result necessitating one of skill to perform an exhaustive search for which locus or loci is/are responsible for determining an individual's OA susceptibility and what minimal combination of those specific loci are required to make a determinative decision with reasonable amount of success whether a person is susceptible or not (and to what degree of susceptibility) to OA as instantly claimed in order to practice the claimed invention.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable.

Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation with no assurance of success.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

- Claims 1-3 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-3 are indefinite for failing to recite a final process step, which agrees back with the preamble in claim 1. While minor details are not required in method/process claims, at least the basic steps must be recited in a positive, active fashion. For example, claim 1 is drawn to a method for identifying individuals susceptible to OA, yet the claim recites a final step merely detecting the presence or absence of a specific allele without any identification of an individual as set forth as a goal of the preamble. No correlation between the action of detecting the allele and susceptibility nor the individual has occurred within method steps. The claims do not set forth the conditions/state when the method has identified individuals susceptible to OA.

Claim 1 is vague and indefinite due to the lack of clarity of the term "susceptible" line 1. The metes and bounds of the parameters that define the varying degrees/levels of susceptibility are unclear within the claims and is absent from the specification. As such claims 2 and 3 are also indefinite.

Specification Objections

The disclosure is objected to because it contains embedded hyperlinks and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code in the specification in the following place: a) page 5, lines 10-13. See MPEP § 608.01.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless

the references have been cited by the examiner on form PTO-892, they have not been considered.

Conclusion

- Claims 1-3 are rejected under 35 U.S.C. 112, first paragraph – enablement.
- Claims 1-3 are rejected under 35 U.S.C. 112, second paragraph.
- Specification objections.
- Information disclosure statement.

No claim is allowed.

Inquiries

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 CFR § 1.6(d)). The central **Fax number is (703) 872-9306**.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Monika B. Sheinberg, whose telephone number is (703) 306-0511. The examiner can normally be reached on Monday-Friday from 9 A.M to 5 P.M. If attempts to reach the examiner by telephone are unsuccessful, the primary examiner in charge of the prosecution of this case, Jehanne Sitton, can be reached at 703-308-6565. If attempts to reach the examiners are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703) 308-1119.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to Patent Analyst, Chantae Dessau, whose telephone number is (703) 605-1237, or to the Technical Center receptionist whose telephone number is (703) 308-0196.

December 29, 2003
Monika B. Sheinberg
Art Unit 1634

MBS

Jehanne Sitton
Primary Examiner
12/29/03
JS